[CASE REPORT]

A Second Case of Sunitinib-associated Pyoderma Gangrenosum

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ABSTRACT

Pyoderma gangrenosum is a painful, noninfectious, ulcerative, cutaneous disorder that most commonly affects the lower extremities. The diagnosis is made by recognizing the characteristic clinical manifestations in the setting of a causative systemic disease and excluding other causes of similar-appearing ulcerations. Pyoderma gangrenosum often evolves in the setting of systemic illnesses, such as inflammatory bowel disease, rheumatological disorders, and hematological conditions. However, several medications have rarely been linked to pyoderma gangrenosum. The authors report the second case of sunitinib-associated pyoderma gangrenosum in a 61-year-old patient with recurrent renal cell carcinoma. (*J Clin Aesthetic Dermatol.* 2010;3(8):34–35.)

A 61-year-old woman with a history of obesity, hypertension, diabetes, and renal cell carcinoma (treated with a remote right nephrectomy) presented with a refractory, painful, right lateral calf ulceration of 11 months duration.

Twelve months prior to her presentation, she was placed on oral sunitinib (37.5mg daily) for recurrent left-sided renal cell carcinoma. One month later, the patient developed a pustule along her distal lateral right calf, which ultimately evolved into a large, painful ulceration. Despite receiving a variety of broad-spectrum oral antibiotics, appropriate compression therapy, frequent wound debridements (office based and intraoperative), and two Apligraf® (Organogenesis Inc., Canton, Massachusetts) applications, the ulceration failed to improve.

A variety of wound cultures yielded no definitive bacterial pathogens. Tissue cultures for fungi and acid fast bacilli were normal. A wound biopsy displayed a neutrophilic infiltrate without evidence of a vasculitis or carcinoma. Noninvasive vascular studies of the lower extremity arteries and veins displayed normal perfusion and no significant reflux, respectively.

Eleven months after the lesion first appeared, the patient presented to the authors' clinic with a large, deep ulceration overlying the right distal lateral calf measuring 4.9 x 4.5cm in diameter and 1.0cm in depth. The base appeared fibropurulent and the margin was noticeably violaceous, partially necrotic, and minimally undermined (Figure 1). Both calves were edematous and the distal pulses were easily palpable.

Sunitinib-provoked pyoderma gangrenosum (PG) ulceration was suspected; consequently, the medication was immediately discontinued. With a regimen of minocycline (50mg BID) and weekly Unna boots (Dynarex Corporation, Orangeburg, New York), the ulceration healed 16 weeks later (Figure 2).

DISCUSSION

The ulcerative neutrophilic dermatosis, PG, frequently presents with an associated condition, such as inflammatory bowel disease, autoimmune disease, or a lymphoproliferative disorder. Rarely has it been documented that medications such as propylthiouracil,[1] granulocyte colony-stimulating factor,[2,3] interferons,[4,5] and antipsychotic drugs induce PG. In 2006, an isolated case of sycosis with PG-like lesions was reported in a patient treated with the tyrosine kinase inhibitor gefitinib.[6]

In 2008, Freyhaus et al[7] reported the index case of sunitinib-associated PG in a 76-year-old woman with a gastrointestinal stromal tumor (GIST).[7] The authors have subsequently documented the second case of this unusual cutaneous side effect of sunitinib.

DISCLOSURE: Drs. Dean and Zirwas report no relevant conflicts of interest.
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Sunitinib is currently approved for the treatment of both GIST tumors resistant or intolerant to imatinib and advanced/metastatic renal cell carcinoma. The medication is a tyrosine kinase inhibitor possessing antitumor and antiangiogenic properties. Additionally, sunitinib inhibits platelet-derived growth factor receptor (PDGFR)-α, FMS-like tyrosine kinase 3 (Flt-3), c-Kit protein, vascular endothelial growth factor receptor (VEGFR)1-3, and colony-stimulating factor receptor 1.

Common cutaneous side effects of sunitinib include hand-and-foot skin reaction (HFSR), alopecia, hair depigmentation, facial erythema, acral erythema, xerosis, and subungual splinter hemorrhages. In a recent review of 119 patients treated with sunitinib, HFSR was the most common cutaneous toxicity occurring in 36 percent of the subjects.[8] The median time to onset of HFSR was 32.4 days. Of interest, the authors' subject developed the premonitory PG pustule approximately four weeks after initiation of sunitinib therapy.

Mechanisms for the development of sunitinib-provoked PG are purely speculative, but may involve keratinocyte alterations via c-kit inhibition[9] and/or VEGFR blockade impairing endothelial cell survival[10] and subsequent capillary repair. It is plausible that the pathergic threshold in PG is lessened by these mechanisms, especially within areas of the body exposed to repetitive microtrauma, such as the lower extremities. Of interest, imatinib, another tyrosine kinase inhibitor, has been linked to several neutrophilic dermatoses, such as Sweet's syndrome and acute generalized exanthematous pustulosis.[11,12] Considering that PG is classified as a neutrophilic dermatosis, it is likely that similar multitargeted kinase inhibition of various proteins and receptors by both sunitinib and imantinib explains the occurrence of comparable cutaneous side effects.[7]

It is important that healthcare providers involved in oncology and specialties likely to deal with lower extremity wounds, such as dermatology, vascular medicine/surgery, podiatry, and wound care, be cognizant of the potential relationship between sunitinib and PG.

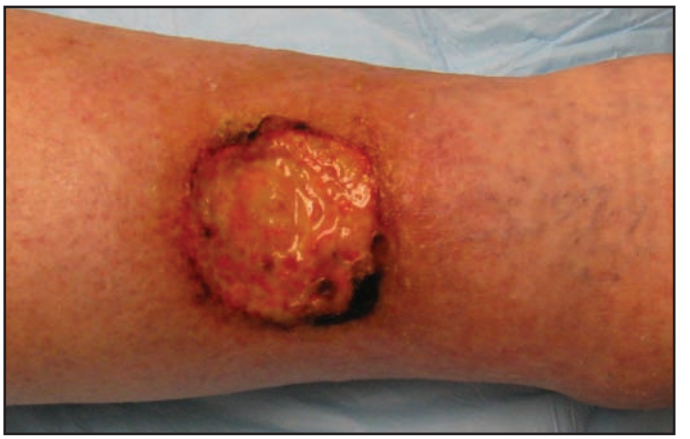

Figure 1. Painful, deep 4.9 x 4.5cm distal lateral calf pyoderma gangrenosum ulceration with a fibropurulent base and violaceous, partially necrotic border

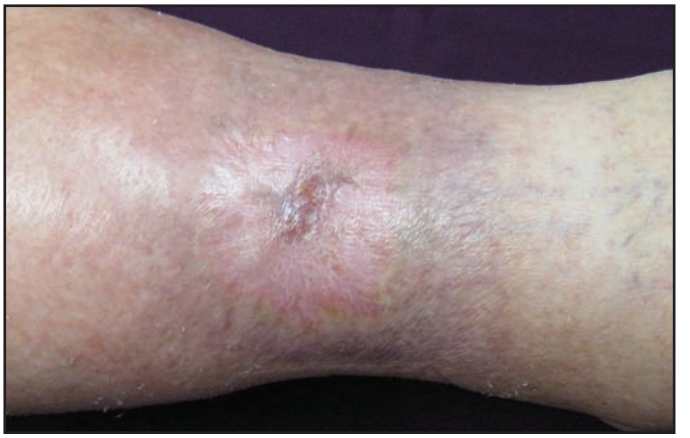

Figure 2. Sixteen weeks after termination of sunitinib, the calf ulceration healed.

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